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Irving H. Goldberg

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THE EFFECT OF WATER LOADING ON THE ANTIDIURESIS OF THE PASSIVE ERECT POSTURE

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B.S. Trinity College 1949

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INTRODUCTION

The rate of flow of urine is the difference between the volume of fluid filtered at the glomerulus and that which is reabsorbed by the tubules (1). This latter, in turn, is conditioned by the magnitude of solute reabsorption, the nature and quantity of the solutes destined for excretion, and the activity of the antidiuretic hormone (ADH) of the posterior pituitary gland which promotes the independent reabsorption of water (1,2,3). It is well established that the secretion of ADH may be stimulated by an increase in the effective osmotic pressure of the extracellular fluid (4) and by emotion (4,5,6). More recently data have accumulated which imply that an increase or decrease in "volume," or some function thereof, may suppress or stimulate the secretion of this hormone (7,8, 9,10,11).

The dilution of the body fluids of a normal subject in the recumbent posture with a volume of water approximately one per cent of the body water will apparently suppress completely the secretion of ADH (12). If this degree of dilution is maintained, the rate of excretion of urine reaches a maximum and the urine is quite dilute. The volume of the urine approximates 10 to 15 per cent of the volume of filtrate. This state is similar to that observed in patients with diabetes insipidus and is referred to as "physiological diabetes insipidus" (4). A further increase in the dilution of body fluids will not augment urine flow.

If a subject in this state of physiological diabetes insipidus is tilted into the passive erect posture (PEP) or has tourniquets applied

to the thighs with a pressure greater than that in the veins, an antidiuresis and antisaluresis will ensue. If the degree of tilt is great enough there will be a decline in the rate of filtration at the glomerulus which may account for part of the decrease in the rates of excretion of water and salt. It seems clear, however, that part of the antidiuresis must be related to secretion of ADH since the decrease in rate of excretion of water is minimal and transient in subjects with diabetes insipidus when they are tilted (13) or have venous occlusive cuffs applied to their thighs (14). There is some evidence that the antisaluresis may, in turn, be conditioned by secretion of adrenal cortical hormone (15). The nature of the stimulus that promotes the ultimate antidiuresis and antisaluresis in these circumstances is not well defined, but the inference is that it is due to a contracted volume or displacement of blood in some key part of the body fluids--probably some part of the vascular system.

This investigation was undertaken to learn whether dilution of the body fluids beyond that necessary to promote complete suppression of secretion of ADH would modify the degree of antidiuresis in the passive erect posture.

HISTORICAL REVIEW

The Role of the Kidney.

Since the kidney is probably the only organ that can facultatively separate water and solutes and thus elaborate a fluid for excretion which is hypertonic or hypotonic to the body fluids, the preservation of the volume and composition of the internal environment devolves upon it. The composition, tonicity, and acid-base relationship of the bladder urine depend upon formation of an ultrafiltrate of the blood at the glomerular membrane and reabsorption in the nephrons (1).

On the basis of direct analyses of fluid from mammalian tubules (16) and micropuncture studies of the tubules of amphibians (17), a topographical order of events in the nephrons has been suggested. Although these concepts of assigning function to specific sites in the tubule have not as yet been demonstrated in the human kidney, various tubular mechanisms will be considered to be distributed in the topographical order as suggested by the available data (16,17).

It appears that about 7/8 of the water and solutes are reabsorbed in the proximal tubules, leaving a solution for delivery to the distal part of the nephron, which is iso- or only slightly hypotonic to the serum (2,16). The solutes are actively reabsorbed in the proximal tubule, creating an osmotic gradient between the tubular lumen and the extracellular fluid which provided for the passive extraction of water in the proximal segment. This has been termed "obligatory reabsorption" by Shannon (3). The volume of water delivered to the

distal tubule, therefore, is a function of the extent to which the solutes have been reabsorbed proximally. The latter depends in part upon the load of solute which is presented to the proximal segment. It will be less if the filtrate contains a high concentration of solutes such as glucose or urea, whose reabsorption is limited. Under conditions of severe dehydration, the rate of urine flow may be diminished even in the absence of the antidiuretic hormone of the posterior pituitary gland (2). This observation may be explained by an accelerated reabsorption of solutes in the proximal tubule or by a decrease in glomerular filtration rate. More recent studies present evidence for nervous control of proximal solute reabsorption (18).

The final volume, composition, and tonicity are determined in the distal tubule, where water and solutes may be treated independently of each other. The reabsorption of water in the distal tubule is active and largely under the control of ADH of the posterior pituitary gland. Under conditions of maximal ADH activity a highly concentrated urine may be produced with an osmolar concentration that may reach 1.4 Osmoles/L. (19). This is conditioned in part by the nature of the solutes and also by the volume of fluid delivered to the distal segment. When large volumes of tubular urine are provided to the distal tubule, the total solutes may be less concentrated despite maximal ADH activity.

Regulation of Water Excretion.

It has been convincingly demonstrated by Verney (4) that the secretion of ADH by the posterior pituitary gland is promoted by

an increase in the effective osmotic pressure of the extracellular fluid bathing a receptor--"osmoreceptor"-- that lies somewhere within the distribution of the internal carotid artery. A small volume of hypertonic saline, sucrose, or dextrose solution--substances which are unable to penetrate the cell membrane by simple diffusion and thus exert an effective osmotic pressure at the membrane--injected into the internal carotid artery of a dog undergoing a water diuresis resulted in a decreased urine flow with an increased urinary solute concentration. This could not be repeated with a substance such as urea which does not exert an effective osmotic pressure because it can diffuse through the cell membrane. The postulated "osmoreceptor," therefore, is stimulated by an increase in effective osmotic pressure or the cellular dehydration this must induce. The stimulus is then transmitted via the supraoptico hypophyseal tract, causing the secretion of ADH of the posterior pituitary gland. An interruption in this nervous pathway has been shown to prevent secretion of this hormone--resulting in a state of diabetes insipidus (20). The converse is also true; a decrease in the effective osmotic pressure bathing the "osmoreceptor" leads to a graded suppression of the secretion by the posterior pituitary gland. The posterior pituitary gland may respond to stimuli other than tonicity, such as emotion (4,5,6) and changes in blood and/or extracellular volume distribution (7,8,9,10,11).

As demonstrated by Welt and Nelson (12), the state of "physiological diabetes insipidus" is characterized by a steady, large flow of urine, a $^U/_P$ ratio of creatinine of approximately eight (indicates that approximately 13 per cent of the filtered water is excreted), and a low

total solute concentration. Once the posterior pituitary gland had been completely suppressed with the subject in the recumbent position, further increase in positive water load, and thus a greater degree of hypotonicity, did not promote any further increase in the rate of excretion of water. Similarly it has been observed by Findley and White (21) that a water load in well-hydrated subjects with diabetes insipidus does not increase the rate of excretion of water. Since current concepts of renal physiology imply that no other mechanism responds to the hypotonicity of body fluids, as far as water excretion is concerned, than inhibition of the secretion of ADH of the posterior pituitary gland, an increase in the rate of urine flow can be achieved only by the delivery of an increased volume to the distal tubule. The latter, as discussed above, depends to a great extent on reabsorption of solutes in the proximal segment. Decreased proximal reabsorption of solute may also result in an increased urine flow and a U/P for creatinine or inulin in the range usually seen in diabetes insipidus. Total solute concentration may also be low.

That tonicity may not be the only stimulus to which the posterior gland can respond has been supported by numerous observations during which increased antidiuretic activity has been demonstrated in the face of hypotonicity. Increased antidiuretic activity in cats rendered hyponatremic by salt depletion has been reported (22). Leaf and Mamby (10) have recently presented evidence for the stimulation of the secretion of ADH under conditions of hypotonicity of the body fluids in response to the insufficiency of volume in a crucial portion of the extracellular

space. Patients with poorly controlled Addison's disease, cases of congestive heart failure with chronic dilution hyponatremia, and normal dogs depleted of salt with contracted extracellular volume exhibited a concentrated urine and a failure to have a prompt water diuresis or dilution of urine upon administration of a water load. The sera of the dogs under such conditions possessed increased antidiuretic activity.

Evidence has been presented that expansion of the plasma volume by the infusion of iso- or hypo-onoctic albumin suppresses the secretion of ADH by the posterior pituitary gland. Welt and Orloff (7) have reported a striking diuresis of water under such conditions with no significant alteration in the rate of excretion of salt or glomerular filtration as measured by the clearance of endogenous creatinine. Since this water diuresis could be inhibited by adding 200 milliunits of posterior pituitary hormone to the infusion, there workers suggested that the diuresis was due to posterior pituitary suppression. This hypothesis has been substantiated by the work of Strauss et al (11), who found no further increase in diuresis in subjects with "physiological diabetes insipidus" who were given iso-oncotic albumin. Strauss et al (9) have shown that the isotonic expansion of extracellular volume in recumbency caused an increased flow of urine with a decreased electrolyte concentration of the urine. Expanded extracellular volume was thought to have resulted in posterior pituitary suppression.

Regulation of Solute Excretion.

The concentration of sodium in the serum has been observed

to play a role in determining its rate of excretion in the urine. Dilution of the body fluids induced by a positive balance of water has been demonstrated to cause a decrease in the rates of excretion of sodium, chloride, and potassium, and an increased rate of excretion of ammonia, in the absence of any consistent change in glomerular filtration. The increased ammonia excretion with dilution was thought to be related to the lesser rate of excretion of sodium and potassium, but could not be correlated with a consistent difference between the rates of excretion of sodium and chloride (23). Marked variations in the rates of excretion of sodium have been observed in the absence of significant changes in the rate at which sodium is filtered through the glomerulus. Such changes must, therefore, be due to alterations in the renal tubular reabsorption of this ion (23,24). However, the errors inherent in the present clearance methods for measuring glomerular filtration rate prevent any accurate apportionment of responsibility to glomeruli or tubules for changes in sodium excretion.

The effective osmotic pressure has been related to the excretion of salt (25,26). The infusion of hypertonic dextrose or mannitol solution in a normal subject promoted an accelerated rate of excretion of salt at the time when the concentration of sodium in the serum was depressed (26). Cellular dehydration induced by the shift of water from the cells to the extracellular compartment owing to the increase in the extracellular effective osmotic pressure may play some part. Goodyer and Glenn (27) have recently demonstrated the direct tubular effects of such solutes when injected into the renal artery of the dog.

The various factors which condition a particular concentration

of sodium in the serum have a significant influence on its excretion. The same concentration of sodium in the serum may be the result of administration of salt to the normally hydrated subject or by the loss from the body of water in excess of salt. The rate of excretion of sodium, however, will be greater in the former than in the latter. This response to a contracted volume has been termed the "dehydration reaction" by Peters (28). The increased reabsorption of salt in the dehydration reaction accentuates ADH secretion by increasing the existing hypertonicity and also saves water by eliminating salt as a solute for excretion. The increase in the rate of excretion of salt associated with the onset of a water diuresis has frequently been attributed to an increasing urine flow *per se*. Crutchfield and Wood (29), however, have observed an inverse correlation between the acceleration in the rate of salt excretion associated with a water diuresis and the rate of urine flow prior to the water loading. As has been shown to occur in the "dehydration reaction," the hydropenic subject has an increased renal tubular reabsorption of salt. This mechanism, however, is depressed when the deficit of water is corrected by a load of water, thus, resulting in an increased rate of excretion of salt. The decrease in salt excretion seen at a later stage of diuresis may be due to a decrease in the concentration of sodium in the serum (23).

The Effect of Erect Posture.

That the flow of urine is less in the erect posture than in the recumbent position was probably described for the first time

at the turn of the century by Wendt, Quincke, and Laehr (30), and soon after was described by Edel (31) and Linossier and Lemoine (32). Erlanger and Hooker (33,34,35) were the first to advance the concept that the antidiuresis of the erect posture was mediated through changes in the renal hemodynamics, considering reduction in pulse pressure in the renal artery as the primary cause for the reduced urine flow. White, Rosen, Fischer, and Wood (36) attributed the increase in the excretion of water and electrolytes in the recumbent position partly to an increased pulse pressure and partly to an increase in renal blood flow and filtration. Ni and Rehburg (37) found that the concentration of serum protein and the oncotic pressure increased in the erect posture. The found, however, using the clearance of exogenous creatinine as a measure of glomerular filtration, that changes in urine flow due to alteration of posture resulted from changes in both filtration and tubular reabsorption. Blegen (38) discovered a close relationship quantitatively and temporally between the total osmotic pressure of the blood and diuresis. Diuresis, following a water load, was delayed in the passive erect posture and started only after the total osmotic pressure of the blood began to fall. Smith (39) stated that the glomerular filtration as measured by inulin clearance and the renal plasma flow as measured by diodrast clearance decreased in the passive erect posture. The resulting increase in the filtration fraction was ascribed to constriction of the efferent glomerular arteriole. Mayerson (40) found a fall in the blood flow in the renal artery in anesthetized dogs in the upright posture on a tilt board. The drop in flow, however, was not as great as in the

femoral or carotid arteries. White and Rolfe (41) observed a diminution in the glomerular filtration rate of 8 per cent in normal subjects upon changing from the supine to the erect posture. The blood flow through the other abdominal viscera has also been shown to diminish (42). More recently Goodyer and Glenn (43) have observed the absence of an effect on urine flow, electrolyte excretion, or clearances of inulin and PAH when pulsation of the renal artery of the dog was partially or entirely eliminated without changing the mean arterial pressure. McCann and Romansky (44,45), recording inulin and diodrast clearances in normal subjects in the recumbent and ordinary erect posture, noted no significant changes in filtration or in renal blood flow. Minimal or no change in the glomerular filtration rate between the recumbent and sitting positions has been reported by Kattus and others (46) and, more recently, by Harrison and his group (47), who also found no change in one patient in the Trendelenberg position.

An increase in the renal venous pressure probably can not be implicated as an important factor in the antidiuresis of the passive erect posture (48,49). The pressure in the inferior vena cava at the level of the renal veins does not rise to the level reported to cause a reduction in urine flow (49). Moreover, Farber, Alexander, and Eichna (50) have demonstrated similar changes in urine and salt excretion in a normal recumbent subject whose vena cava was obstructed either above or below the renal veins.

Brun, Knudsen, and Raaschou (51) investigated the antidiuresis induced in normal subjects by the assumption of the passive erect posture (PEP). In order to eliminate muscular activity as a force in aiding

venous return, the subjects were suspended by their perineums in a saddle-like arrangement with their lower limbs dangling free. They found a definite antidiuresis of 20-40 per cent of the initial urine flow when the subjects had been in the PEP at an angle of +60° with the horizontal for one hour. Increase in the U/P for inulin and in the urine specific gravity were observed (51 I). The antidiuresis was sustained for some time after the subjects had returned to the recumbent posture. The inulin clearance which had fallen approximately 20 per cent in the PEP rose rapidly after tilting back to the horizontal. As a rule the inulin and diodrast clearances fell to lower levels the longer the stay in the erect position and the greater the angle of tilt (51 II). As has been demonstrated before (37,52,53), these investigators found that concentration occurs in the blood as soon as the subject is tilted to the PEP. Whereas those at +40° showed a 5-10 per cent increase very early, subjects tilted at +20° for one hour exhibited no hemoconcentration. The changes in filtration and plasma flow were attributed mainly to constriction of the efferent glomerular arteriole. The authors suggested, however, that the increased reabsorption of water might be due to the action of the ADH of the posterior pituitary gland.

Much evidence has been presented which emphasizes the importance of distribution as well as the magnitude of blood volume in the regulation of secretion of ADH by the posterior pituitary gland. Epstein, Goodyer, Lawrason, and Relman (8) confirmed the previous findings of contraction of plasma volume, decrease in renal clearances, antinatriuresis and antidiuresis in quiet standing. These workers were able to reverse the antidiuresis of the PEP without increasing the

rate at which sodium is filtered by the administration of hypertonic saline with its associated increase in plasma volume. Rapid infusions of albumin resulting in slight expansion of the plasma volume, however, failed to reverse the antidiuresis of quiet standing. Strauss and his associates (9) have shown that, whereas isotonic expansion of extracellular volume in recumbency caused an increased flow of diluted urine, in the sitting posture an equal expansion did not significantly diminish antidiuretic activity.

The assumption of the PEP tends to pool the blood in the lower extremities. Lack of muscular activity in the lower limbs, resulting in diminished venous and lymphatic return, intensifies the pooling. The PEP decreases both the absolute and effective blood volumes of the circulation by increasing capillary filtration pressure, resulting in transudation of fluid into the tissues of the lower limbs. The transudation accounts for the hemoconcentration which has been reported. The antidiuresis and antinatriuresis, however, precede the hemoconcentration and actual reduction in absolute blood volume, but may be correlated with change in distribution of blood from the cranium to the limbs. By immersing the body in water up to the level of the heart or by applying pneumatic occluding cuffs to the legs, the antidiuresis of the erect posture can be modified (53,54).

That the secretion of ADH by the posterior pituitary gland is concerned in the antidiuresis of the PEP is evidenced by the fact that subjects with diabetes insipidus react to the PEP with a transient and much less marked antidiuresis than normal subjects. Judson and his associates (14) observed similar findings in subjects with diabetes

insipidus in whom simulated passive erect posture was produced by experimental venous congestion of the limbs. Antidiuresis and diminished sodium excretion, however, have been demonstrated in normal subjects following venous congestion of the legs (55). The presence of antidiuretic activity in the blood of a subject maintained in the passive erect posture has been demonstrated by Brun, Hilden, and Raaschou (13) by the induction of antidiuresis in a normal recumbent subject, undergoing water diuresis, by injection of the blood of the tilted person. The blood of a subject with diabetes insipidus maintained in the erect posture for a similar length of time failed to produce a similar response.

The upright posture reduces the rate of excretion of salt in the urine (8,9,47,56). The studies of Harrison et al (47,56) have presented evidence for the existence in the cephalad portion of the body of receptors which are able to respond to changes in "effective blood volume." These workers have demonstrated that compression of the neck by a cuff inflated to a pressure of 20 mm. of mercury in a normal subject in the sitting posture was partially effective in overcoming the antinatriuresis of the upright posture. The failure to secure consistent changes in the rate of urine flow by neck compression, however, may be accounted for by the stimulation of secretion of ADH induced by the discomfort of the procedure. The changes in sodium excretion induced in normal subjects by change in posture and by compression of the neck were independent of filtration and were thus attributed to alterations in tubular activity. In both recumbent and sitting positions, with or without neck compression, the excretion of chloride paralleled

that of sodium, but no consistent variation in potassium excretion was noted except for the decline in urinary potassium which appeared in both positions after the first four or five hours of ingesting potassium-free loading solution. In view of the failure of neck compression to cause a further decrease in potassium excretion, it was considered unlikely that the increased excretion of sodium was mediated through the adrenal cortex. Welt (15), however, has presented evidence that the increased salt reabsorption of the passive erect posture is mediated via the adrenal cortex. He found that the antisaluresis of the passive erect posture in the subject with Addison's Disease is not marked and is transient in nature. Harrison and his group (47) observed no consistent alterations in sodium excretion in the subject in the Trendelenberg position with the foot of the bed elevated approximately twenty degrees. No rise in sodium excretion occurred as the result of neck compression in recumbent subjects. The same investigators have demonstrated that the antinatriuresis induced by the venesection of 2-5 cc. of blood per kilogram of body weight from sitting subjects can be prevented by compression of the neck (57). Recent studies by Lombardo and Harrison (58) have failed to show an increased excretion of sodium in the urine of patients with congestive heart failure in the sitting position after neck compression. The effect of posture on the excretion of salt and water is markedly reduced in patients with congestive heart failure. Lombardo (59) has suggested that the previously postulated volume regulating mechanism in the head is either inactive or overshadowed in patients with congestive heart failure.

Welt and Orloff (7) have shown that increases in the plasma volume by as much as 89 per cent by infusion of iso-oncotic albumin are not associated with increase in the urinary excretion of sodium above its "control" level. Recently, Strauss et al (11) have shown that the hypotonic expansion of the extracellular fluid in normal recumbent, water-loaded subjects augments the urinary excretion of sodium despite a diminished filtered load. Since no effect was observed with a similar expansion of extracellular volume in the sitting position, it was suggested that changes in extracellular volume or some associated factor in the cephalad portion of the body serve as the stimulus for sodium retention or excretion. Epstein, Post, and McDowell (60) have recently demonstrated increased renal excretion of sodium upon occlusion of the arteriovenous fistula. There was no associated change in glomerular filtration rate, renal blood flow or renal venous pressure. These data further suggest conditioning of renal excretion of sodium by the degree of filling of some portion of the arterial tree.

Effect of Oncotic Pressure.

Still another factor independent of volume or tonicity has been demonstrated to influence the excretion of salt and water. Goodyer, Petersen, and Relman (61) and Welt and Orloff (7) have provided evidence that the infusion of hyperoncotic solutions of salt-poor albumin induces a decreased rate of salt excretion in normal subjects. The increased reabsorption of salt is not mediated via the adrenal cortex since it was observed in a subject with Addison's Disease. The antidiuresis promoted by the rise in the oncotic pressure has been demonstrated by

Petersdorf and Welt (63) to be independent of the secretion of the antidiuretic hormone of the posterior pituitary gland since it occurred in patients with diabetes insipidus. Water reabsorption was secondary to sodium reabsorption. The existence of an oncoreceptor somewhere within the vascular tree which would respond in a graded fashion to changes in oncotic pressure has been postulated (7,63).

Nervous Control of Tubular Function.

The content of the cranial vault has been implicated indirectly in the regulation of excretion of salt and water by the renal tubules, if only by virtue of the residence therein of the osmoreceptor of Verney, the postulated volume receptor, and the posterior pituitary body. That the nervous system may play a more direct role in the preservation of the composition and volume of the body fluids, independent of its influence on water and salt consumption, has been presented in a most convincing manner.

Polyuria associated with an increased urinary salt excretion despite restricted salt and water ingestion has been induced by experimental lesions in the medulla. Bilateral interruption of the splanchnic nerves to the kidneys reproduced these findings (63). Marshall and Kolls (64 I and II) demonstrated that unilateral renal denervation resulted in an increased excretion of water and salt by the denervated kidney with no significant change in the glomerular filtration rate. These same workers presented evidence implicating the renal nerve supply in the direct control of tubular reabsorption of salt independent of changes in renal hemodynamics (64 III and V). Recently the studies of

Kriss, Futcher, and Goldman (65) and Kaplan and Rapaport (66) have substantiated the thesis of a direct neural regulation of renal tubular function in the dog. Localization of this process to the proximal segment of the nephron has been suggested (66). A syndrome characterized by the wasting of salt in the urine in the face of depressed electrolyte concentrations in the serum has been described in patients with disease of the central nervous system by Welt, Peters, et al (18,67). Two patients with this picture of cerebral salt-wasting demonstrated an apparently normal anterior pituitary-adrenal axis as determined by normal eosinopenic response to epinephrine and marked increase in excretion of 17-ketosteroids in response to the administration of ACTH. The marked negative balance of potassium in response to desoxycorticosterone and ACTH administration, despite the relatively small overall positive balance of sodium which was actually negative in some periods, has been interpreted as indicating that increased reabsorption of salt has taken place in the distal tubule (18,68). It is concluded, therefore, that the defect in cerebral salt wasting is in the proximal tubular absorption of salt which is of such a magnitude as not to be easily overcome by increasing tubular salt reabsorption presumably via the adrenal cortex.

EXPERIMENTAL PROCEDURE AND METHODS

A. Experimental Procedure.

The experimental subjects in these studies were 5 normal male graduate students. There were a total of 10 studies, consisting of 5 paired studies. Food, water, and tobacco were restricted for a period of 8 to 14 hours prior to and throughout each experiment. In order to make up for salt losses due to warm weather in those studies done in the summer, salt was ingested in increased amounts to avoid salt depletion in the few days prior to each study. In studies 7-10 there was no prior added salt intake. In studies 5 and 6, 5 grams of NaCl were ingested on the day prior to the experiment; in studies 1,2, and 4, 5 grams of NaCl per day were ingested for 2 days prior to the experiment; in study 3, 5 grams per day were ingested for 3 days.

Each subject presented himself at the laboratory at about 8 AM at which time he voided the overnight specimen, which was used as the inulin blank. He was then weighed and weighed again at the end of the experiment. A sample of blood was obtained and an infusion of 5 per cent or 3 1/2 per cent glucose in water was started at a rate adequate to achieve the desired positive balance of water. A priming dose of inulin was administered in a different vein on the same arm, and the sustaining infusion of inulin in 5 per cent glucose solution was started. The primary dose was calculated on the basis of an "inulin" space of approximately 15 per cent of the body weight with a desired serum concentration of approximately 20 to 30 mg. per cent

of inulin. The concentration of inulin in the infusion and the rate of administration of water with inulin were determined according to estimated glomerular filtration rate and insensible water loss for the individual on the day of the experiment. The subjects remained in the horizontal position until the desired positive balance of water and a relatively steady state of urine flow were reached, but they were permitted to stand to void. Urines were obtained by spontaneous voidings at approximately 30 to 60 minute intervals. Subsequent blood samples were drawn from the other arm by means of an indwelling Cournand needle so as to avoid painful vena punctures with consequent antidiuretic effect.

Upon completion of the initial water loading and upon reaching a state of physiological diabetes insipidus in recumbency, the subjects were tilted—still lying supine on the tilted table—to an angle of 15° with the horizontal with the head raised up and the lower limbs completely relaxed. A tilt angle of 15° was used in order to minimize renal hemodynamic changes. Where it was thought necessary to increase the load rapidly with a minimum of initial glycosuria (studies 4 and 6), 3 1/2 per cent glucose in water was used. In study 4, 100 units of Pitressin were given at the start of the experiment in order to provoke retention of a greater proportion of the administered water.

In general, blood was drawn according to the following plan:

1. Initial sample before start of infusions.

2. Specimen for determination of the concentration of inulin in the serum about one hour after the priming dose had been administered and the sustaining infusion had been started. This is a

time when equilibrium of inulin has been achieved.

3. Sample near the time of tilting.

4. Sample near the time of maximal antidiuresis in the passive erect posture.

5. Sample at the termination of the study.

Each study began at about 8 AM and lasted from 7 to 13 hours.

Two studies were performed on each subject. Except in studies 1 and 2—subject J.M.—where the water loads at the time of maximum antidiuresis were approximately the same, each subject received a small water load (but still greater than one per cent of body water) at one time—the lightly-loaded study and a heavy water load the next time (equal to about twice the first water load)—the heavily-loaded study.

B. Determinations.

Blood was collected under oil, and that used for hemoglobin and hematocrit determination was defibrinated anaerobically immediately after collection. Urine samples were placed in covered bottles containing benzoic acid. All samples were stored in the refrigerator.

Hemoglobin measurements were made colorimetrically as alkaline oxyhemoglobin (69). Cell volumes were determined in quadruplicate in Doland hematocrit tubes, calibrated in per cent (70). Concentrations of sodium and potassium in serum and urine were determined in the flame photometer (71). Serum chloride concentration was determined using the Eisenman semi-micro modification of the Volhard-Harvey method (72), and the concentration of chloride in the urine was determined by the Volhard-Harvey technique (73). Total protein concentration in the serum was determined by a biuret method (74). The

concentration of glucose in the serum was determined colorimetrically by the Somogyi-Nelson technique (75). Qualitative determinations of urine sugar were obtained using Benedict's solution with 2 to 3 times the usual 8 drops of urine. Urine ammonias, and ureas were determined by the diffusion methods described by Conway (76). The photometric method using resorcinol as proposed by Roe, Epstein, and Goldstein (77) was used for the determination of inulin in the plasma and urine.

C. Calculations.

The total osmolarity of urine was calculated from the equation:

1) $2\ (\mathrm{Na} + \mathrm{K} + \mathrm{NH_3}) + \mathrm{Urea}$ (m.Osm./L.)

The total osmolarity of the extracellular water (EW) was calculated from the equations:

2) a. $2\ (\mathrm{Na_{EW}} + \mathrm{K_{EW}}) + 10$

for the initial blood

b. $2\ (\mathrm{Na_{EW}} + \mathrm{K_{EW}}) + 10 + \Delta$ glucose

for subsequent specimens, since the concentration of glucose was always somewhat higher.

The percentage change in plasma volume was calculated from the formulae:

3) $$\frac{PV_2}{PV_1} = \frac{Hgb_1}{Hgb_2} \times \frac{1 - Hkt_2}{1 - Hkt_1} \times 100$$ (69) (studies 1-6)

where Hgb = hemoglobin and Hkt = cell volume.

4) $$\frac{TP_1}{TP_2} \times 100$$ (studies 7-10)

where TP = total protein in grams per cent.

Glomerular filtration rate was estimated by the clearance of exogenous inulin and was calculated by the formula:

$$5)\quad C_{In} = \frac{UV}{S}$$

where C_{In} = clearance of inulin, U = concentration of inulin in the urine, S = concentration of inulin in the serum, and V = rate of excretion of urine in cc. per minute. The concentration of inulin in the serum at the mid-point of the clearance period was determined by plotting the concentration of inulin in serum against time on a semi-logarithmic graph. The rate of excretion of inulin per minute was corrected for the rate of excretion of inulinoid material as estimated from the urine blank.

As a measure of water reabsorption the inulin U/S ratio was calculated where U and S are the concentration of inulin in urine and serum respectively.

The balance of water at the end of any urine period may be calculated using the formulae:

$$6)\quad I.L._{H_2O} = \frac{\left[I_t - (U_t + B_t)\right] - (W_2 - W_1)}{T}$$

where $I.L._{H_2O}$ = insensible loss of water in cc. per minute, I_t = total volume of infusate (glucose solution + insulin solution) in study, U_t = total volume of urine in the study, B_t = total volume of blood withdrawn multiplied by the specific gravity of blood, W_2 = weight at end of study, W_1 = weight at start of study, T = total duration of study in minutes.

$$7)\quad bH_2O = I_p - \left[(I.L._{H_2O} \times t) + U_p + B_p\right]$$

where bH_2O = balance attained during a particular urine period in cc., I_p = infusate (glucose solution + inulin solution) during that period in cc., t = duration of that period in minutes, U_p = urine volume in cc. during that period, B_p = cc. of blood x specific gravity of blood withdrawn during that period.

The total balance of water at the end of any period is equal to the sum of the balances of the preceding urine periods.

The concentration of water in serum $[W]_s$ was calculated from the concentration of serum proteins $[P]$:

$$8)\quad [W]_s = 98.4 - 7.18\,[P] \qquad (78)$$

The concentration of Na in extracellular water (E), was calculated from the serum concentration S by use of a Donnan factor of 0.95 and the serum water $[W]_s$.

Thus:

$$9)\quad [Na]_E = \frac{[Na]_s \times 0.95}{[W]_s} \qquad (78)$$

The concentration of potassium in extracellular water was assumed to be equal to that of serum. ($K_E = K_s$).

The concentration of increased reabsorbate promoted by the passive erect posture may be determined from the formulae:

$$10)\quad \text{for Na: } \frac{\Delta \text{ rate of excretion Na/min.}}{\Delta \text{ rate of excretion urine/min.}}$$

$$11)\quad \text{for total solutes: } \frac{\Delta \text{ rate of excretion total solutes/min.}}{\Delta \text{ rate of excretion urine/min.}}$$

This is valid only if the glomerular filtration rate and the filtered load are comparable.

The osmolar clearance of water (Cosm) was calculated from the formula:

$$12)\quad Cosm = \frac{Uosm}{Posm} V \qquad (79)$$

where Uosm = total m.Osm./L. in urine, Posm = total m.Osm./L. in plasma, V = urine flow (cc./min.).

The urine flow, V, is given by the sum:

$$13)\quad V = Cosm + C_{H_2O}$$

where C_{H_2O} = clearance of free water,

and therefore

$$14)\quad C_{H_2O} = \left[1 - \frac{Uosm}{Posm}\right] V \qquad (79).$$

RESULTS

I. The Effects of Water Loading on Plasma Volume (Table I and Table A - appendix).

Plasma volume as measured by changes in hemoglobin and hematocrit (studies 1-6) or by changes in concentration of serum protein (studies 1-10) was altered to varying degrees. Except for blood period III in study 3 which exhibited an insignificant negative variation, as measured by hematocrit and hemoglobin, the other studies showed slight to moderate increases in plasma volume during the course of the experiments. The greatest increase observed was that of 32.3 per cent in period III in study 6. No correlation existed between the magnitude of the positive balance of water and the change in plasma volume. Changes in plasma volume between the pre-tilt period and the period of maximal antidiuresis were small.

The decrease in plasma volume upon assumption of the passive erect posture, which has previously been reported (8,51,52,54,80-82) was not observed under conditions of water loading and the 15° PEP. Duration of time in the passive erect posture had no consistent effect on the plasma volume in these studies.

II. Effects on the Concentration of Electrolytes in the Body Fluids (Table I and Table A - appendix).

The infusion of glucose solution consistently resulted in a decrease in the concentration of the electrolytes in the extracellular fluid. The absolute value of the depression and the percentage change in serum sodium concentration were dependent upon the magnitude

Table I

The Effects of Water Loading on the Plasma Volume, Serum Sodium Concentration, and Total Solute Concentration in the Extracellular Fluids in PEP

Study	Subject	Date	Time at End of Per. of Max. Antid.	Balance H_2O	% ΔPV		Concentration of Serum Na			Total Solute Conc. EW		
							Abs.	Δ	%Δ	Abs.	Δ	%Δ
				cc.	%		mEq./L.		%	mOsm/L.		%
					*	**	***	†	†	***	†	†
1	J.M.	8/5	377	657	+11.1	+10.1	138.3	-3.7	-2.6	300.9	-6.5	-2.1
2	J.M.	7/16	409	625	+12.3	+8.3	137.5	-3.8	-2.7	298.9	-7.3	-2.4
3	T.G.	7/14	627	1539	+10.4	+10.7	139.4	-8.8	-5.9	301.3	-18.5	-5.8
4‡	T.G.	8/7	522	2523	+4.8	+10.7	132.9	-8.6	-6.1	289.2	-16.2	-5.3
5	W.J.	8/25	445	959	+26.1	+22.0	136.9	-6.2	-4.3	297.0	-12.2	-3.9
6‡	W.J.	9/2	752	1947	+25.8	+18.6	131.0	-10.8	-7.6	284.6	-22.2	-7.2
7	E.B.	12/23	373	759		+13.7	137.9	-3.5	-2.5	287.0	-8.0	-2.6
8‡	E.B.	12/29	440	1702		+11.0	135.4	-6.3	-4.4	293.0	-11.8	-3.9
9	W.D.	1/12	501	760		+7.0	143.5	-1.9	-1.3	306.6	-4.2	-1.4
10‡	W.D.	1/19	496	2015		+13.0	136.1	-6.7	-4.7	295.4	-11.2	-3.7

*Calculated from Hgb. and Hkt.

**Calculated from concentration of total protein.

***Concentration at time of maximum antidiuresis.

† Change from beginning of study to time of maximum antidiuresis.

‡ The heavily loaded study of the pair.

of the water load in the lightly-loaded and heavily-loaded studies of the paired experiment, except in studies 3 and 4. In study 3 the subject presented himself with a serum sodium concentration of 148.2; whereas in study 4, his initial serum sodium was 141.6. In study 3, therefore, the extracellular fluid volume was probably decreased owing to dehydration preceding the experiment. In study 3 a water load, smaller than that of its companion study, produced an absolute fall in serum sodium concentration of about the same absolute value (study 3, 148.2 → 139.4 at maximal antidiuresis; study 4, 141.6 → 132.9 at maximal antidiuresis). The percentage change in serum sodium concentration (study 3: -5.9 per cent; study 4: -6.1 per cent) varied only slightly between the two studies. Moreover, the percentages of change in total solute concentration in the extracellular fluid from the beginning of the study to the time of maximal antidiuresis were only slightly different (study 3: -5.8 per cent; study 4: -5.3 per cent). The absolute level of the sodium concentration of the serum and the total solute concentration in the extracellular fluid were, however, much lower in study 4 than in study 3. Any difference in degree of antidiuresis in these two studies might, therefore, conceivably be related to the absolute value of sodium concentration in the serum or, more properly, to the total "effective" solute concentration in the extracellular fluid.

Depressions in serum chloride concentration tended to follow the alteration in serum sodium concentration. Serum potassium concentrations usually decreased. In studies 5, 9 and 10, however, increases in serum potassium concentration were noted. The changes observed, however, were within the error of the method of potassium determination.

The glucose concentration in the serum was increased during the initial loading, leading to a transient overflow of sugar in the urine. With rapidly increasing efficiency of utilization of glucose by the body, however, glucose levels were maintained below the renal threshold. In study 3, however, because of augmentation in the rate of infusion of glucose in water, 1+ spillage (using 2-3 x amount of urine) was detected at about the time of maximal antidiuresis.

III. Effects of Glomerular Filtration Rate (Table II and Table B - appendix).

Neither maintenance of the positive load of water in the recumbent or in the passive erect postures had any consistent effect on the rate of glomerular filtration as measured by the clearance of exogenous inulin. No definite difference in glomerular filtration rates can be noted between the period of urine collection just preceding the tilting and the time of maximal antidiuresis. The glomerular filtration rates of the lightly-loaded and heavily-loaded studies of each paired study were comparable--considering the error inherent in the method of inulin clearance determination.

Unlike the studies of Brun, Raaschou, and Knudsen (51), no decrease in GFR was observed in these studies as the duration of time in the passive erect posture increased.

IV. Effects of Dilution of Body Fluids and Posture on the Excretion of Water (Tables II and B - appendix).

Once the positive load of water had reached approximately

Table II

The Effects of Water Loading on the Rates of Water, Sodium and Total Solute Excretion, Clearances and U/P Ratios for Inulin, and Change in Total Solute Concentration in the Urine in Recumbency and PEP

Study	Subject	Date	C_{Inulin}		Rate of Excretion of H_2O				Rate of Excretion of Na				Rate of Excretion of Total Solutes				$\Delta U/P_{In.}$	Δ Concentration of Total Solutes in Urine
			P.T.	M.A.	P.T.	M.A.	Δ	%Δ	P.T.	M.A.	Δ	%Δ	P.T.	M.A.	Δ	%Δ		
			cc./min.			cc./min.		%	µEq./min.			%	µOsm./min.			%	%	%
1	J.M.	8/5	180.0	180.0	20.3	14.5	-5.8	-28.6	185.0	105.7	-79.3	-42.8	898	688	-210	-23.4	+31.3	+7.2
2	J.M.	7/16	207.6	202.0	19.3	15.2	-4.1	-21.2	181.0	117.0	-64.0	-35.4	931	754	-177	-19.0	+23.6	+2.9
3	T.G.	7/14	130.2	123.9	10.3	4.5	-5.8	-56.7	138.0	63.2	-74.8	-54.3	669	433	-236	-35.3	+120.0	+49.5
4*	T.G.	8/7	130.0	135.0	19.8	16.8	-3.0	-15.4	162.8	127.8	-35.0	-21.5	768	656	-112	-14.6	+22.6	+1.0
5	W.J.	8/25	140.9	145.5	15.2	9.0	-6.2	-40.5	189.0	83.4	-105.6	-55.8	839	572	-267	-31.8	+73.5	+14.4
6*	W.J.	9/2	139.0	125.7	10.6	8.2	-2.4	-22.2	81.9	46.5	-35.4	-43.3	561	426	-135	-24.1	+16.2	-2.4
7	E.B.	12/23	102.0	101.5	18.7	13.4	-5.3	-28.3	121.6	77.0	-44.6	-36.7	755	598	-177	-23.4	+38.8	+10.7
8*	E.B.	12/29	95.6	107.0	21.1	18.3	-2.8	-13.3	103.3	60.4	-42.9	-41.5	692	538	-154	-22.3	+28.6	-10.4
9	W.D.	1/12	135.0	126.0	18.4	10.2	-8.2	-44.5	230.0	127.5	-102.5	-48.9	955	692	-263	-29.5	+68.3	+30.4
10*	W.D.	1/19	123.0	125.0	16.3	14.1	-2.2	-13.6	145.1	91.7	-53.4	-36.8	766	654	-112	-14.6	+17.9	-1.3

*Heavily loaded study of the pair.

P.T. Pre-tilt period.

M.A. Period of maximum antidiuresis.

All changes are calculated from pre-tilt period to period of maximum antidiuresis.

one per cent of the total body water, no further increase in the rate of urine flow was observed by increasing the water loading in recumbency in any study. Except for paired studies 3 and 4, and 5 and 6, the rate of excretion of water in the period just preceding the tilt was of approximately similar value for the same subject with the small and greater water loads. In lightly-loaded study 3, the rate of excretion of urine was 10.3 cc./min.; whereas, in heavily-loaded study 4, the rate for this same period was 19.8 cc./min. The reverse situation obtained in paired studies 5 and 6. In lightly-loaded study 5, the urine flow was 15.2 cc./min. during the pre-tilt period; whereas, that of heavily-loaded study 6 was 10.6 cc./min. Study 6 was extremely unusual in that it took 487 minutes from the start of the experiment to reach an equilibrium of urine flow in the recumbent position. In this study following a profuse glycosuria and heavy loss of solutes on attempting to get in a large water load with 5 per cent glucose in water, the excretion of sodium promptly decreased and was associated with the diminished urine flow. It seems unlikely, however, that the urine flow can be correlated with the salt excretion in study 3. In this study the urine flow was 10.4 cc./min. when the sodium excretion was 165 μOsm./min. and 10.9 cc./min. when the sodium excretion was 210.6 μOsm./min. In its paired study when the sodium excretion was 162.8 μOsm./L., the urine flow was 19.8 cc./min. In all three instances the glomerular filtration rate remained approximately the same. In all other studies, moreover, a steady state of flow of urine was maintained in recumbency in the face of a

decreasing sodium or total solute excretion rate.

In every case, assumption of the passive erect posture was accompanied by a decrease in the rate of excretion of urine. The degree of maximal antidiuresis, in terms of percentage change in urine flow in the urine period preceding the tilting and that at the time of maximal antidiuresis in the PEP, was related to the extent of dilution of body fluids in the lightly-loaded and heavily-loaded studies of each paired study. In any paired study, the greater the positive balance of water, the less was the degree of maximal antidiuresis. The antidiuresis associated with the PEP was modified by the extent of dilution, insofar as the concentration of sodium in the serum or, particularly, the concentration of total "effective" solutes in the extracellular fluid were decreased to a greater extent by the larger than by the smaller water load (Tables I and II).

The water loads in studies 1 and 2 were approximately the same at the time of maximum antidiuresis (study 1 -657 cc.; study 2 -625 cc.). The concentrations of sodium in the serum and total solutes in the extracellular fluid were likewise approximately the same. The percentages of maximum antidiuresis in these two studies, therefore, also were in the same range (study 1 -28.6 per cent; study 2 -21.2 per cent).

The time required to reach the period of least urine flow in the PEP showed no consistent correlation with the degree of water loading, although in studies 1 and 2, and 5 and 6, upon tilting, the urine flow fell more rapidly with the smaller load.

In every case, except 5 and 6, in which pre-tilt urine flows differed from each other, the absolute rates of urine flow in the period of maximal antidiuresis were greater in the studies with the greater dilution than in the lightly-loaded studies.

V. Effects on the Reabsorption of Water in the Tubules.

That a smaller percentage of filtered water is being reabsorbed by the tubules in the study with the greater dilution of the pair is also indicated by the changes in U/P for inulin and concentration of total solutes in the urine (Table II and Table B - appendix). The U/P_{In} uniformly increased upon assumption of the PEP. In the study with the heavy water load, the percentage increase of the U/P_{In} of the period of maximal antidiuresis over that in the pre-tilt period is less than that in the lightly-loaded study. Similarly, the concentration of total solutes in the urine at the time of maximal antidiuresis is less in absolute amount and in percentage change from the pre-tilt period (and is sometimes actually negative) when the dilution is greater.

Since the glomerular filtration rate and the filtered load were constant in the pre-tilt period and the period of maximal antidiuresis, the ratios of the change in rate of sodium or total solute excretion to the change in rate of water excretion represent the characteristics of the increased reabsorbate due to the PEP (Table III). In each instance these are quite hypotonic reabsorbates. If the antidiuresis of the PEP were due to increased proximal reabsorption of solute, this increased reabsorbate should be isosmotic with the filtrate.

Table III

The Effects of Water Loading on the Increased Reabsorbate of the PEP

Study	$\frac{*\Delta\ \text{Eq. Na Excr./Min.}}{*\Delta\ \text{cc. } H_2O\ \text{Excr./Min.}}$	$\frac{*\Delta\ \text{Osm. Tot. Sol. Excr./Min.}}{*\Delta\ \text{cc. } H_2O\ \text{Excr./Min.}}$
1	13.67	36.20
2	15.60	43.17
3	12.90	40.69
4**	11.67	37.30
5	17.03	43.06
6**	14.75	56.25
7	8.42	22.60
8**	15.30	55.00
9	12.50	13.66
10**	24.27	120.20

* Δ between pre-tilt and maximum antidiuretic periods.

** Heavily loaded study of pair.

Table IV

The Effects of Water Loading on the Osmolar Clearance of Water and the Clearance of Free Water in the PEP

Study		$C_{Osm.}$	$\Delta C_{Osm.}$	C_{H_2O}	ΔC_{H_2O}	ΔC_{H_2O}
			cc./min.			%
1	P.T.	3.0		17.3		
	M.A.	2.3	-.7	12.2	-5.1	-29.5
2	P.T.	3.1		16.2		
	M.A.	2.5	-.6	12.7	-3.5	-21.6
3	P.T.	2.2		8.1		
	M.A.	1.4	-.8	3.1	-5.0	-61.7
4*	P.T.	2.6		17.2		
	M.A.	2.3	-.3	14.5	-2.7	-15.7
5	P.T.	2.8		12.4		
	M.A.	1.9	-.9	7.1	-5.3	-42.7
6*	P.T.	2.0		8.6		
	M.A.	1.5	-.5	6.7	-1.9	-22.1
7	P.T.	2.5		16.2		
	M.A.	2.0	-.5	11.4	-4.8	-29.6
8*	P.T.	2.4		18.7		
	M.A.	1.8	-.6	16.5	-2.2	-11.8
9	P.T.	3.1		15.3		
	M.A.	2.3	-.8	7.9	-7.4	-48.4
10*	P.T.	2.6		13.7		
	M.A.	2.2	-.4	11.9	-1.8	-13.1

* Heavily loaded study of pair.

P.T. Pre-tilt period.

M.A. Period of maximum antidiuresis.

All changes are calculated from pre-tilt period to period of maximum antidiuresis.

Since it is hypotonic, water was reabsorbed in excess of solutes and probably independently.

Using the calculations as proposed by Wesson and Anslow (79), it may be seen in Table IV that the osmolar clearance of water changed insignificantly in the PEP and that the decrease in urine flow is due to a decrease in the clearance of free water. The decrease in clearance of free water with the PEP is less with the larger water load.

VI. Effects on the Excretion of Electrolytes (Table II and Table B - appendix).

The greater the dilution of the body fluids, the less was the rate of excretion of sodium, chloride, and total solutes in the urine in both recumbency and the PEP. This was true of all studies except 3 and 4, where the reverse obtained.

Except in studies 3 and 4, the rate of excretion of potassium was less in the study with the larger water load. Ammonia excretion uniformly increased with the greater degree of dilution.

These results are similar to those observed by Darragh, Welt, Goodyer, and Abele (23) in recumbent subjects with increased dilution of the body fluids.

Assumption of the PEP resulted in a further decrease in the rates of excretion of sodium and chloride in all studies. Potassium excretion in the PEP showed no consistent trend. Changes were seen in both directions and were usually small in magnitude. Urinary ammonia excretion increased in every study in the PEP. The rate of excretion of urea decreased in all studies during the antidiuresis of the PEP.

Unlike water diuresis, the rate of excretion of sodium in the urine in recumbency depends upon the degree of dilution of body fluids induced by the positive load of water in excess of one per cent of body water. Therefore, when comparing the percentage change in antinatriuresis between the pre-tilt and maximal antidiuretic periods in the lightly-loaded and heavily-loaded studies, account is taken of the concentration of sodium in the serum during these periods in addition to whatever other factors may be operative (Table A). By the maintenance of similar loads of water in both periods, the serum sodium concentrations differed only slightly in the two periods in all studies (0 to 0.7 per cent change in Na_s concentration) except 3 and 4. This factor, therefore, would not account for any difference in percentage change of antinatriuresis which might be observed between the lightly-loaded and the heavily-loaded studies. In study 3 the per cent change in serum sodium concentration was -0.71 per cent (140.4 → 139.4 mEq./L.); in study 4 it was -2.35 per cent (136.1 → 132.9 mEq./L.). The antinatriuresis between the above two periods in study 3 was -54.3 per cent, whereas, that in study 4 was -21.5 per cent. This paired study, however, as has already been pointed out, was also different in that in the study with the greater dilution, the rate of excretion of sodium in the urine was also greater than its companion.

As may be seen in Table II the difference in the percentage antisaluresis between the pre-tilt and maximal antidiuretic periods was less marked than the difference in the percentage antidiuresis.

In studies 7 and 8, moreover, there was actually a greater percentage antinatriuresis with the larger water load.

VII. Effect of Painful Stimulus.

In an unpaired study not reported in these experiments there was a marked antidiuresis from 18.9 to 11.8 cc./min. following a painful venapuncture. This occurred despite a 10 per cent increase in the glomerular filtration rate. In the next urine period the urine flow increased to 16.6 cc./min. The rate of excretion of sodium decreased from 118.2 to 98.0 µOsm./min., but the rate of excretion of potassium increased from 40.3 to 51.4 µOsm./min. Ammonia excretion also increased from 54.8 to 63.2 µOsm./min. As a consequence, total solute excretion increased slightly. These data imply a probable terminal tubular effect mediated via the adrenal cortex and the posterior pituitary gland.

In study 4, about 2 hours before the termination of the study by nausea and vomiting, the patient began to complain of "fullness of the stomach" which was said to disappear after a few minutes but was followed in the last urine period by nausea and subsequent vomiting after collection of the urine. The period prior to the last one, therefore, was used to represent the period of maximal antidiuresis. Since this study was the one with the greater water load of the pair, the antidiuresis thus obtained is probably falsely high. The difference in the percentage of maximal antidiuresis between these two studies is probably even more significant.

DISCUSSION

These studies confirm the findings of others that a decrease in the rates of excretion of water and salt occurs in the passive erect posture. It was possible, however, by increasing the positive water load to modify the antidiuresis of the passive erect posture. The percentage of maximal antidiuresis was consistently of a smaller magnitude in the study of each paired group in which the positive load of water, or more properly, the degree of dilution of body fluids was greater. The fact that a smaller per cent of filtered water was being reabsorbed in the renal tubules was also indicated by the smaller percentage increase in U/P for inulin in those studies with the greater dilution.

Once the state of "physiological diabetes insipidus" had been attained in the recumbent posture, a steady state of urine flow was maintained despite further increase in the positive balance of water. Further increase in hypotonicity beyond that point required to completely inhibit the secretion of the antidiuretic hormone of the posterior pituitary, resulted in no increase in urine flow. When the subject assumed the passive erect posture, however, there was an associated decrease in the rates of excretion of salt and water. The antidiuresis and antisaluresis so produced are thought to be due to the independent handling of these materials in the distal tubule. The transient and less marked antidiuresis, and antisaluresis observed in subjects with diabetes insipidus (13) and adrenal insufficiency (15), respectively, support this hypothesis. The diminished rate of urine

flow, therefore, has been attributed to the stimulation of secretion of ADH by the posterior pituitary gland by a stimulus of decreasing "effective volume." That absolute volume is probably not as important a factor as the distribution of volume is indicated in these studies in which plasma volume was actually mildly increased in the passive erect posture. These data support the findings of other workers (8,9).

It is seen in these studies, therefore, that the posterior pituitary gland which had been completely suppressed by one stimulus, tonicity acting via the osmoreceptors, was stimulated to secrete its antidiuretic hormone by a second stimulus, "volume," perhaps acting via volume receptors strategically located intracranially. The data indicate that under conditions in which the "volume" stimulus is active in producing antidiuresis, a further increase in the positive balance of water now is able to modify the antidiuresis so produced. The antidiuresis in the 15° PEP was modified to a greater extent than the antisaluresis.

Possible explanations may be proposed:

I. The effect on the antidiuresis:

1. By modifying a decrease in the glomerular filtration rate.

2. By variations in proximal tubular reabsorption of salt.

3. By modifying the stimulus to secretion of ADH, by
    a. sustaining "volume" better
    b. greater degree of hypotonicity suppressing the secretion of ADH which had been stimulated by the "contracted volume" promoted by the passive erect posture.

Evaluation of the proposed explanations:

1. The modifying effect of the larger water load was not due to its influence on the glomerular filtration rate (Table II). Although only very small changes in filtration rate may produce relatively large changes in rates of excretion of water and solute, variations of the order noted in these studies are within the experimental error of the present inulin clearance methods (2).

2. If the antidiuresis were to be explained by an increase in the proximal tubular reabsorption of solutes with its accompanying obligatory reabsorption of water, the increment of reabsorbate should be isosmotic with the filtrate. Actually, this increment of reabsorbate appears to be distinctly hypotonic both with respect to sodium and total solutes (Table III). This implies that water was reabsorbed in excess of solutes in this increment of reabsorbate. In order to explain the antidiuresis as an increase in proximal tubular reabsorption under these circumstances, then, one would have to add one or both of two additional mechanisms:

a. less distal reabsorption of salt during the maximal antidiuretic period as compared with the pre-tilt period, or

b. distal tubular secretion of water.

a. is most unlikely and there is no evidence for b. Moreover, to explain the difference in the degree of the antidiuresis with small and large water loads, one would have to postulate that a larger water load promoted less proximal salt reabsorption.

The data from other investigations plus the data from these studies imply that the antidiuresis is the result of independent reabsorption

of water--presumably due to the secretion of ADH by the posterior pituitary gland. Wesson and Anslow (79) point out that the water of the final urine represents an isosmotic fluid which has been either concentrated by the abstraction of water without solutes or diluted by the abstraction of solutes without water. Of the total urine flow there are, therefore, two fractions: 1) a volume that would contain the excreted solutes in a concentration isosmotic with the filtrate. This is called the osmolar clearance of water, and 2) a volume of water that is free of solutes--this value, in turn, will be negative if water has been abstracted in excess of solutes and positive if solutes have been reabsorbed in excess of water. (On theoretical grounds and under certain circumstances, this clearance of free water might conceivably represent secreted water). The calculations in Table IV reveal: 1) that virtually all the decrease in urine flow with the PEP is due to a decrease in the clearance of free water (presumably via ADH action), and 2) that the decrease in clearance of free water with the PEP is less with the larger water loads.

3. The question then arises as to whether the lesser secretion of ADH with the larger water loads is related to the fact that a) the larger water loads support volume better and, therefore, the PEP is associated with a lesser "contraction of volume" or b) the greater degree of hypotonicity modifies the response of the posterior pituitary gland to the same intensity of stimulus represented by the "contracted volume" of the PEP.

a. Volume

"Better support of volume" with the larger water loads would have to be expressed as a greater increase in extracellular fluid volume or plasma volume. It is unlikely that the antidiuresis of the PEP or venous occlusion is related to the contraction of the extracellular volume as a whole, because extracellular volume as a whole does not contract. However, there is likely a redistribution of interstitial fluid so that more is located in the lower half of the body. This would take some time to effect, whereas the antidiuresis of the PEP or cuffing comes on quite rapidly.

We look, therefore, to a volume that does change rapidly in these circumstances, and that, of course, is the plasma volume. This is redistributed to some extent immediately and then contracts in absolute terms due to the increased rate of transudation. If one examines the plasma volume changes in the lightly- and heavily-loaded studies, however, there is no evidence that plasma volume was better supported with the larger as compared with the smaller water loads (Table I). This does not exclude this possibility, however, since the change in volume might well be more subtle than the techniques which were used to measure them.

b. Greater degree of hypotonicity

There was a greater degree of hypotonicity with the large as compared with the small loads in every instance--both in percentage change and in actual magnitude. It might well be that this is, in fact, the influence that modified the responsiveness of the posterior pituitary gland to the stimulus to secrete antidiuretic hormone.

II. The effect on antisaluresis:

The difference in percentage antisaluresis was less marked than the difference in percentage of antidiuresis (Table II), and in one instance, E.B., there was actually a greater percentage antisaluresis with the larger water load.

When the differences in percentage of antisaluresis associated with the PEP in the paired studies is examined statistically, it is found that $t = 1.98$ and p is greater than 0.1--which is usually not considered statistically significant. When the differences in percentage of antidiuresis are similarly treated, it is found that $t = 3.75$, making $p =$ between .05 and .01, which is highly significant. Therefore, it would be quite difficult to explain the difference in the degree of antidiuresis on the associated changes in salt if these latter changes were not significantly different in the lightly- and heavily-loaded studies.

SUMMARY AND CONCLUSIONS

1) The effect of water loading on the rates of excretion of water and electrolytes was studied in normal young adult males in the recumbent position and in the passive erect posture (PEP) with the head elevated at 15° with the horizontal. Two studies were performed on each subject. In one study the subject received a small water load (lightly-loaded study), and in the other he received a large water load (heavily-loaded study).

2) The rates of excretion of water and salt decreased in the 15° PEP.

3) By increasing the load of water in the body beyond one per cent of body water, it was possible to modify the antidiuresis of the passive erect posture. The percentage of maximum antidiuresis was decreased by increasing the load of water in the body.

4) The modifying effect of the larger water load was not due to its influence on glomerular filtration rate.

5) The modifying effect of the larger water load was not due to any effect on proximal tubular solute reabsorption.

6) There is no evidence that plasma volume was better supported by the larger than by the smaller water loads.

7) There was a greater degree of hypotonicity of the body fluids with the larger than with the smaller water load.

8) It is suggested that hypotonicity of the body fluids may be the influence which modified the response of the posterior pituitary to the passive erect posture.

9) Statistical analysis revealed that the antisaluresis induced by the passive erect posture was not affected by the degree of water loading.

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Table A (appendix)

The Effect of Water Loading on the Concentrations of Protein and Electrolytes in Serum and the Volume of Body Fluids in Recumbency and PEP

Study	Subject	Date	Blood Period	Time	Whole Blood			Concentration in Serum						$\frac{TP_1}{TP_2}$ x 100
					Hgb.	Hkt.	$\frac{PV_2}{PV_1}$	Na	K	Cl	T.P.	Glucose	Inulin	
				min.			%	mEq./L.			gm.%	mg.%	mg.%	
1	J.M.	8/5	I	19	12.3	36.5	100.0	142.0	4.00	106.2	7.20	76		100.0
			II	95									30.4	
			**III	155	11.7	35.3	107.1	139.3	3.48	105.4	6.53	110	21.6	110.1
			IV	215	11.9	36.5	103.4	139.3	3.60	105.7	6.77	100	21.4	106.2
			†V	370	11.1	36.3	111.1	138.3	3.44	103.3	6.53	143		110.1
2	J.M.	7/16	I	15	12.2	38.0	100.0	141.3	4.35	108.0	6.96	94		100.0
			II	103									35.2	
			**III	165	11.6	36.5	107.9	138.2	4.11	108.2	6.53	150	26.0	106.5
			†IV	319	11.2	36.0	112.3	137.5	3.96	106.2	6.42	136	21.4	108.3
			V	468	10.9	35.8	115.8	135.8	3.58	106.2	6.20	160	22.4	112.1
3	T.G.	7/14	I	18	14.5	43.1	100.0	148.2	4.13	108.2	7.05	91		100.0
			II	123									26.2	
			**III	246	14.3	44.3	99.6	140.4	3.85	104.0	6.72	115	27.0	104.8
			†IV	616	13.6	41.3	110.4	139.4	3.75	102.0	6.36	118	22.6	110.7
4*	T.G.		I	15	13.7	41.0	100.0	141.6	3.73	106.2	6.96	93		100.0
			II	120									36.0	
			**III	270	13.4	41.0	102.2	136.1	3.25	101.4	6.36	111	22.6	109.4
			IV	346	12.9	40.0	108.0	133.0	2.63	99.0	5.78	139	17.6	120.4
			†V	565	13.1	40.9	104.8	132.9	2.83	97.6	6.28	175	21.6	110.7
5	W.J.	9/2	I	10	14.3	44.0	100.0	143.1	3.74	103.2	7.30	70		100.0
			II	135									40.4	
			**III	275	12.6	42.0	117.6	136.4	4.07	100.0	5.86	145	23.6	124.5
			†IV	455	12.5	38.3	126.1	136.9	4.03	100.0	5.98	117	21.6	122.0

[*] Heavily loaded study of the pair.

[**] Blood drawn near time of tilting.

† Blood drawn near time of maximum antidiuresis.

Table A (appendix)

Study	Subject	Date	Blood Period	Time	Whole Blood			Concentration in Serum						$\frac{TP_1}{TP_2}$ x 100
					Hgb.	Hkt.	$\frac{PV_2}{PV_1}$	Na	K	Cl	T.P.	Glucose	Inulin	
				min.			%	mEq./L.			gm.%	mg.%	mg.%	
6*	W.J.	9/2	I	15	13.5	42.1	100.0	141.8	4.00	104.8	7.10	73		100.0
			II	110				131.9	3.65			321	32.0	
			**III	480	11.1	37.0	132.3	131.0	3.31	97.6	5.47	110	16.2	129.7
			IV	680	11.4	39.2	124.2	131.4	3.38	96.8	5.82	74	12.8	122.0
			†V	755	11.4	38.5	125.8	131.0	3.38	96.6	5.98	134	13.2	118.6
7	E.B.	12/23	I	10				141.3	4.3	101.8	6.40	81		100.0
			II	101				137.6	3.9	101.8	5.71	169	32.0	112.0
			**III	172				136.7	4.2	100.7	5.58	189	30.6	114.7
			IV	287				139.9	3.8	101.9	5.81	114	31.0	110.6
			†V	436				139.0	3.8	101.5	5.63	120	33.4	113.7
8*	E.B.	12/29	I	8				141.7	4.0	101.8	6.31	63		100.0
			II	94				136.7	4.5	98.5	5.38	144	27.6	117.3
			**III	169				132.9	3.5	98.7	5.19	132	26.2	121.5
			IV	324				135.7	3.5	97.6	5.38	131	25.8	117.3
			†V	441				135.4	3.6	98.6	5.69	117	22.2	110.0
9	W.D.	1/12	I	10				145.4	3.9	104.1	5.75	83		110.0
			II	99				142.3	4.0	103.8	5.00	179	23.2	115.0
			**III	194				141.2	3.7	105.0	5.05	126	23.8	114.0
			IV	327				141.0	4.0	103.9	5.13	129	23.8	112.0
			†V	506				143.5	4.3	102.3	5.35	112	25.8	107.0
10*	W.D.	1/19	I	7				142.8	4.0	103.6	6.10	83		100.0
			II	85				137.5	4.4	102.2	5.30	145	27.6	115.0
			**III	179				138.3	4.7	101.4	5.40	150	26.3	113.0
			IV	419				136.1	4.2	100.2	5.40	145	25.0	113.0
			†V	555				137.7	4.5	98.6	5.70	164	23.8	107.0

*Heavily loaded study of the pair.
**Blood drawn near time of tilting.
†Blood drawn near time of maximum antidiuresis.

Table B (appendix)

The Effects of Water Loading on Clearances, Concentrations, and Rates of Excretion of Solutes in Urine in Recumbency and PEP

Study	Subj. Date	Time at end of Urine Pd.	Time of Tilt	Urine Vol.	Concentration in Urine							Rates of Excretion in Urine							C_{In}	U/P In	+b H_2O
					Na	K	Cl	NH_3	Urea	Total Sol-utes	Inu-lin	H_2O	Na	K	Cl	NH_3	Urea	Total Sol-utes			
				cc.	m.Osm./L.						mg.%	cc./min.	μOsm./min.						cc./min.		cc.
1	J.M. 8/5	86		450	48.6	9.28	45.4	6.46	56.0	184.6		5.23	254.0	48.6	238.0	33.8	293	966			847
		149		1195	11.3	1.80	9.95	2.69	20.4	51.1	243	19.0	215.2	34.2	189.0	51.3	387	970	178.0	9.4	984
		180	185	630	9.11	1.68	8.46	2.32	18.0	44.2	176	20.3	185.0	34.1	172.0	47.1	366	898	180.0	8.9	772
		212		510	8.22	2.46	8.20	2.39	18.5	44.6	192	15.9	131.0	39.2	130.6	38.1	295	711	161.0	10.2	674
		313		1500	7.25	2.83	7.10	3.11	19.8	46.2	224	14.9	107.7	42.1	105.5	46.2	294	686	178.0	11.9	504
		377		930	7.28	2.64	6.50	3.93	19.7	47.4	242	14.5	105.7	38.4	94.5	57.1	286	688	180.0	12.4	657
2	J.M. 7/16	100		620	48.6	15.60	48.7	4.51	74.5	211.8		6.2	301.5	96.5	302.0	28.0	462	1313			509
		164		1285	11.87	3.00	10.9	2.32	28.6	63.0	289	20.1	238.0	60.3	219.0	46.6	575	1266	189.9	9.45	415
		192	194	540	9.38	1.74	8.95	2.49	21.1	48.3	276	19.3	181.0	33.6	173.0	48.0	407	931	207.6	10.75	487
		222		570	8.92	1.75	8.46	2.64	25.0	51.6	255	19.0	170.0	33.2	161.0	50.1	475	981	196.5	10.34	472
		282		1115	8.50	1.74	8.01	2.84	23.2	49.4	254	18.6	158.0	32.3	149.0	52.7	430	917	202.9	10.92	428
		311		510	8.48	1.59	7.60	3.15	22.8	49.2	263	17.6	149.0	28.0	134.0	55.5	401	866	210.3	11.94	447
		376		1040	7.36	1.87	6.22	3.27	22.5	47.5	274	16.0	118.0	29.9	99.6	52.4	360	760	203.0	12.69	486
		409		500	7.71	2.15	5.66	3.70	22.6	49.7	292	15.2	117.0	32.6	85.9	56.1	343	754	202.0	13.29	625
		442		530	7.14	1.98	5.28	3.85	22.4	48.3	318	16.1	115.0	31.8	84.8	61.9	360	776	230.8	14.33	834
		475		530	6.69	2.06	5.03	3.79	20.3	45.4	282	16.1	107.5	33.1	80.7	60.9	326	730	202.8	12.60	1016
3	T.G. 7/14	120		455	44.53	10.48	48.8	9.38	77.2	206.0	835	3.79	169.0	39.8	185.1	35.6	293	781			1140
		177		620	19.35	3.13	18.9	2.84	29.2	79.8	326	10.9	210.6	34.1	205.8	30.9	318	868	134.6	12.4	1318
		241		665	15.85	2.66	14.5	2.41	26.0	67.8	332	10.4	165.0	27.6	150.8	25.1	270	705	129.1	12.4	1179
		301	306	620	13.35	2.82	12.1	2.78	26.8	64.7	336	10.3	138.0	29.2	125.0	28.7	277	669	130.2	12.6	1186
		416		625	19.50	4.53	17.5	5.70	45.4	104.9	570	5.43	106.0	24.6	95.1	31.0	247	570	121.4	22.4	1468
		513		680	11.43	4.30	8.56	4.75	32.1	73.1	432	7.01	80.1	30.2	60.0	33.3	225	513	124.9	17.8	1367
		627		510	14.13	6.12	12.2	7.62	41.0	96.7	639	4.50	63.2	27.4	54.6	34.1	184	433	123.9	27.7	1539

——— Time of tilting to 15° PEP.

* Heavily loaded study of the pair.

Table B (appendix)

Study	Subj. Date	Time at end of Urine Pd.	Time of Tilt	Urine Vol.	Concentration in Urine							Rates of Excretion in Urine							C_{In}	U/P In	+b H_2O
					Na	K	Cl	NH_3	Urea	Total Sol-utes	Inu-lin	H_2O	Na	K	Cl	NH_3	Urea	Total Sol-utes			
				cc.	m.Osm./L.						mg.%	cc./min.	µOsm./min.						cc./min.		cc.
4*	T.G. 8/7	115		635	57.0	11.8	62.5	7.38	61.6	346.8		5.52	314.6	65.2	345	40.6	340	1914			2303
		237		2635	14.3	1.85	12.3	1.94	16.47	52.65	173	21.1	301.5	39.0	260	40.9	347	1110	121.2	5.74	1912
		268		635	9.20	1.53	7.70	1.73	15.88	40.80	142	20.5	188.5	31.3	158	35.4	325	836	123.0	6.00	1935
		299	304	615	8.21	2.11	7.10	1.66	14.76	38.72	142	19.8	162.8	41.9	141	32.9	293	768	130.0	6.55	1849
		340		735	7.78	2.24	6.81	1.99	15.50	39.52	142.5	17.9	139.5	40.2	122	35.7	278	710	133.0	7.42	2086
		411		1300	7.90	2.27	6.10	2.02	15.26	39.64	146	18.3	144.6	41.6	112	37.0	280	726	146.8	8.02	2203
		483		1255	7.69	2.09	5.64	2.26	15.16	39.24	152	17.4	134.0	36.5	98.4	39.4	264	682	136.6	7.83	2418
		522		655	7.61	1.95	5.64	2.51	14.95	39.09	164	16.8	127.8	32.8	94.8	42.2	251	656	135.0	8.03	2523
		562		625	9.55	1.63	5.98	2.46	14.69	41.97	190	15.6	149.2	25.5	93.4	38.5	230	656	140.7	9.00	2706
5	W.J. 8/25	87		730	26.8	5.40	26.6	4.96	39.8	104.1		8.39	225.0	45.4	223	41.6	334	874			1238
		139		870	10.19	2.31	9.15	2.18	19.1	48.46	410.5	16.73	170.3	38.6	153	36.4	320	810			700
		183		640	10.30	3.46	9.41	2.09	22.3	54.00	349.5	14.55	149.9	50.4	137	30.4	324	785	139.2	9.56	909
		231		810	11.36	3.25	9.24	1.59	18.6	51.00	238.5	16.89	191.7	54.8	156	26.8	314	861	131.7	7.80	819
		266	283	530	12.48	3.75	10.35	1.75	19.4	55.36	242.5	15.20	189.0	56.8	157	26.5	294	839	140.9	9.29	947
		313		670	10.33	3.35	8.30	2.48	19.4	51.72	229.5	14.26	147.2	47.8	118	35.4	276	737	139.8	9.80	881
		378		640	8.59	4.66	9.24	3.91	24.4	58.72	336	9.85	84.6	45.9	91.0	38.5	240	579	145.0	14.74	961
		445		605	9.24	5.15	8.98	4.09	26.4	63.36	356	9.02	83.4	46.5	81.0	37.0	238	572	145.5	16.11	959
6*	W.J. 9/2	92		650	29.90	7.03	34.80	4.87	45.5	129.1		7.06	211.5	49.6	246	34.4	322	912			1828
		178		2102	14.70	2.14	15.20	1.47	15.8	52.42	148	24.4	359.0	52.3	372	35.9	386	1280	118.3	4.85	1924
		223		670	6.91	3.71	9.24	2.30	16.3	42.14	175	14.9	103.0	55.3	138	34.2	243	627	96.2	6.45	2105
		273		670	6.47	5.06	9.41	2.35	20.2	47.96	180	13.4	86.7	67.8	126	31.5	271	642	97.4	7.26	2170
		337		715	6.49	5.83	10.40	3.21	21.8	52.86	225	11.18	72.5	65.1	116	35.8	244	591	112.2	10.04	2013
		406		715	8.57	4.53	8.72	4.00	22.8	57.00	249	10.37	88.9	47.0	90.4	41.4	236	591	130.0	12.53	2105
		487	491	855	7.76	3.99	7.70	4.03	21.6	53.16	228	10.60	81.9	42.1	81.3	42.5	228	561	139.0	13.18	1977
		577		860	6.21	4.72	7.70	4.56	21.6	52.58	213	9.55	59.4	45.2	73.6	43.6	206	503	133.0	13.91	1943
		665		730	5.60	5.08	7.86	5.29	22.4	54.34	225	8.29	46.5	42.2	65.2	43.9	186	451	135.1	16.30	1988
		752		714	5.66	5.08	8.04	5.05	20.3	51.88	199	8.20	46.5	41.7	66.0	41.4	167	426	125.7	15.31	1947

——— Time of tilting to 15° PEP.

* Heavily loaded study of the pair.

Table B (appendix)

Study	Subj. Date	Time at end of Urine Pd.	Time of Tilt	Urine Vol.	Concentration in Urine							Rates of Excretion in Urine							C_{In}	U/P In	+b H_2O
					Na	K	Cl	NH_3	Urea	Total Sol-utes	Inu-lin	H_2O	Na	K	Cl	NH_3	Urea	Total Sol-utes			
				cc.	m.Osm./L.						mg.%	cc./min.	µOsm./min.						cc./min.		cc.
7	E.B.	96		405	25.3	10.4	25.6	6.73	70.7	155.6		4.2	106.3	43.7	107.5	28.3	296.9	638			641
	12/23	169		1252	7.4	3.5	6.1	1.93	21.4	47.1	182	17.2	127.3	60.2	104.9	33.2	368.1	810	99.0	5.76	596
		191		415	6.9	2.8	6.3	1.99	18.4	41.8	160	18.9	130.1	52.9	119.1	37.6	347.8	790	98.8	5.24	652
		212		400	6.5	2.7	6.0	1.97	18.3	40.6	164	19.0	123.5	51.3	114.0	37.4	347.7	772	102.0	5.34	683
		233	236	392	6.5	2.5	6.1	2.06	18.2	40.3	168	18.7	121.6	46.8	114.1	38.5	340.3	755	102.0	5.46	752
		258		440	6.7	2.5	6.2	2.13	18.1	40.8	168	17.6	117.9	44.0	109.1	36.3	318.6	719	95.7	5.44	687
		284		425	5.0	2.6	5.4	2.43	18.7	38.8	185	16.3	81.5	42.4	88.0	39.6	304.8	633	97.3	5.96	686
		373		1193	5.7	3.6	5.4	2.85	20.6	44.7	238	13.4	77.0	48.3	72.5	38.2	276.0	598	101.5	7.58	759
		403		410	5.9	3.8	6.0	3.30	20.6	46.6	236	13.7	80.8	52.1	82.2	45.2	282.2	639	99.5	7.26	780
		432		425	4.8	3.3	5.5	3.00	18.7	40.9	206	14.7	70.6	48.5	80.9	44.1	274.9	602	91.8	6.24	693
8*	E.B.	89		335	24.3	7.0	27.0	10.50	40.3	123.9		3.8	92.3	26.6	106.2	39.9	153.0	471			1715
	12/29	189		2102	4.9	2.0	5.5	2.46	15.4	34.1	128	21.0	102.9	42.0	115.5	51.7	323.0	716	101.0	4.79	1679
		228		785	4.3	2.0	5.0	2.37	14.6	28.9	128	20.1	86.4	40.2	100.5	47.6	293.0	581	98.6	4.90	1732
		248	251	422	4.9	1.9	5.6	2.35	14.5	32.8	118	21.1	103.3	40.1	118.2	49.6	306.0	692	95.6	4.54	1772
		271		460	4.6	1.7	5.0	2.55	13.7	31.4	120	20.0	92.0	34.0	100.0	51.0	274.0	628	92.4	4.62	1698
		296		475	4.2	2.1	3.9	2.85	13.9	32.2	130	19.0	79.8	39.9	74.1	54.2	264.0	612	95.4	5.01	1675
		320		450	3.8	2.1	4.3	2.89	14.2	31.8	130	18.8	71.4	39.5	80.8	54.3	267.0	598	94.8	5.04	1727
		345		473	3.6	2.2	4.0	2.90	13.9	31.3	134	18.9	68.0	41.6	75.6	54.8	263.0	592	99.4	5.26	1730
		369		455	3.5	2.1	3.6	2.76	11.7	28.4	130	19.0	66.5	39.9	68.4	52.4	222.0	540	99.6	5.24	1727
		393		445	2.7	2.1	4.2	3.00	12.9	28.5	134	18.5	50.0	38.9	77.7	55.5	239.0	527	103.0	5.59	1771
		415		450	3.2	2.2	4.1	3.11	12.1	29.1	140	20.5	65.6	45.1	84.1	63.8	248.0	597	123.0	6.00	1755
		440		458	3.3	2.1	4.1	3.14	12.3	29.4	134	18.3	60.4	38.4	75.0	57.5	225.0	538	107.0	5.84	1702

——— Time of tilting to 15° PEP.
* Heavily loaded study of the pair.

Table B (appendix)

Study	Subj. Date	Time at end of Urine Pd.	Time of Tilt	Urine Vol.	Concentration in Urine							Rates of Excretion in Urine							C_{In}	U/P In	+b H_2O
					Na	K	Cl	NH_3	Urea	Total Solutes	Inulin	H_2O	Na	K	Cl	NH_3	Urea	Total Solutes			
				cc.	m.Osm./L.						mg.%	cc./min.	µOsm./min.						cc./min.		cc.
9	W.D.	93		455	24.6	3.2	25.8	8.6	71.7	144.5		4.9	120.5	15.7	126.4	42.1	351.0	708.1			705
	1/12	127		565	9.0	1.0	10.1	2.9	19.4	45.2	176	16.6	149.4	16.6	167.7	48.1	322.0	750.3	126	7.59	640
		191		1110	12.0	1.4	12.8	2.3	18.3	49.7	174	17.3	207.6	24.2	221.4	39.8	316.6	859.8	128	7.40	625
		222	228	570	12.5	2.9	13.1	1.8	17.5	51.9	174	18.4	230.0	53.4	241.0	33.1	322.0	955.0	135	7.32	530
		253		490	15.2	4.7	17.3	2.1	18.8	62.8	172	15.8	240.2	74.3	273.3	33.2	297.0	992.0	114	7.23	565
		288		540	13.9	3.9	14.7	2.6	20.4	61.2	184	15.4	214.1	60.1	226.4	40.0	314.2	947.5	119	7.74	625
		323		430	12.5	5.2	15.0	2.8	21.1	62.1	226	12.3	153.8	64.0	184.5	34.4	259.5	763.8	117	9.50	715
		366		550	11.6	4.7	12.9	3.0	21.5	60.1	224	12.8	148.5	60.2	165.1	38.4	275.2	769.3	120	9.39	820
		412		485	11.0	4.1	12.4	3.7	22.8	60.4	262	10.5	115.5	43.1	130.2	38.9	239.4	634.2	113	10.73	915
		501		905	12.5	5.0	13.8	4.6	23.5	67.7	310	10.2	127.5	51.0	140.8	46.9	239.7	690.5	126	12.30	760
10*	W.D.	82		335	18.7	4.2	22.8	11.4	95.3	163.9		4.1	76.7	17.2	93.5	46.7	390.7	672.0			1440
	1/19	175		1510	7.1	1.5	8.4	2.7	25.1	47.7	182	16.8	119.3	25.2	141.1	45.4	421.7	801.4	113	6.75	1615
		263		1395	7.5	1.6	10.0	3.5	24.0	49.2	198	15.9	119.3	25.4	159.0	55.7	381.6	782.3	121	7.59	1900
		320	320	930	8.9	2.2	10.6	3.3	18.2	47.0	194	16.3	145.1	35.9	172.8	53.8	296.7	766.0	123	7.55	1920
		348		450	8.6	2.6	10.6	3.3	22.5	51.5	184	16.1	138.5	41.9	170.7	53.1	362.3	829.2	116	7.22	1905
		380		505	8.3	2.8	10.6	3.4	21.9	50.9	192	15.8	131.1	44.2	167.5	53.7	346.0	804.0	119	7.56	1890
		410		456	7.3	2.5	9.6	3.7	20.0	47.0	204	15.0	109.5	37.5	144.0	55.5	300.0	705.0	122	8.13	1850
		438		405	6.6	2.6	8.7	4.1	19.3	45.9	218	14.5	95.7	37.7	126.2	59.5	279.9	665.6	127	8.73	1910
		496		815	6.5	2.5	8.0	4.2	20.0	46.4	218	14.1	91.7	35.3	112.8	59.2	282.0	654.0	125	8.90	2015
		523		385	5.6	2.5	7.2	4.3	20.6	45.4	216	14.3	80.1	35.8	103.0	61.5	294.5	649.2	128	8.93	2065
		553		440	4.9	2.5	6.5	4.2	18.5	41.7	202	14.7	72.0	36.8	95.6	61.7	272.0	613.0	124	8.41	2095

——— Time of tilting to 15° PEP.

* Heavily loaded study of the pair.

Date Due

Demco 293-5

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